UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,122	09/11/2006	Brenda M. Ogle	07039-463US1	4639

26191 7590 01/23/2009

FISH & RICHARDSON P.C.
PO BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
01/23/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/554,122	OGLE ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13-17* is/are pending in the application.

4a) Of the above claim(s) *9,10,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed October 17, 2008. Claims 1-50 were previously pending, with claims 9, 10 and 16-50 withdrawn from consideration. Applicants cancelled claims 11, 12 and 18-50 and amended claims 1, 7, 9, 10, 14, 15 and 17. Claims 9, 10, 16 and 17 remain withdrawn. Claims 1-8 and 13-15 will be examined.

2. Applicants' amendments overcame the following rejections: rejection of claims 1-3, 6 and 13-15 under 35 U.S.C. 102(b) as being anticipated by Wagner et al.; rejection of claims 1-3, 6 and 13-15 under 35 U.S.C. 102(b) as being anticipated by Yoshida et al.; rejection of claims 1-3, 6, 7 and 13-15 under 35 U.S.C. 102(b) as being anticipated by Lebed et al.; rejection of claims 4, 5, 7 and 8 under 35 U.S.C. 103(a) over Wagner et al. and Fulton et al.; rejection of claims 4, 5, 7 and 8 under 35 U.S.C. 103(a) over Yoshida et al. and Fulton et al.; rejection of claim 8 under 35 U.S.C. 103(a) over Lebed et al. and Allen et al. The rejection of claim 11 (now incorporated into claim 1) under 35 U.S.C. 103(a) over Lebed et al. and Wang et al. is maintained for reasons given in the response to arguments below.

3. This office action presents new grounds for rejection necessitated by amendment.

Response to Arguments

4. Applicant's arguments filed October 17, 2008 have been fully considered but they are not persuasive.

Regarding the rejection of claim 11 under 35 U.S.C. 103(a) over Lebed et al. and Wang et al., Applicants argue that Lebed et al. do not disclose labeled RNA molecules or the need to detect low-abundance mRNAs, therefore there would have been no motivation to combine the two references.

However, Lebed et al. disclose that there are possibly 10^6 to 10^7 different TCR transcripts (page 818, third paragraph; page 821, last paragraph), the abundance of which changes in diseased tissues, as discussed by Lebed et al. (page 818, first paragraph). Considering that the total RNA used for amplification was 300ng (page 814, fourth paragraph), a standard RT-PCR might not be sufficient to amplify low-abundance transcripts, as it is biased towards 3'-end amplification, as pointed out by Wang et al. Therefore one of ordinary skill in the art would be motivated to use the aRNA of Wang et al. instead of the cDNA of Lebed et al. for the determination of transcripts with low abundance.

The rejection is maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejections based on the Yoshida et al. reference

6. Claims 1-3, 6-8 and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al. (Immunogenetics, vol. 52, pp. 35-45, 2000; cited in the previous office action) and Mahadevappa et al. (Nature Biotechnol., vol. 17, pp. 1134-1136, 1999).

A) Regarding claim 1, Yoshida et al. teach a method for determining lymphocyte diversity in a subject, said method comprising

a) providing labeled nucleic acid molecules from a population of said subject's lymphocytes, wherein each said labeled nucleic acid molecule encodes a lymphocyte receptor or a portion thereof (page 36, fifth, sixth and seventh paragraph; page 37, first and second paragraph);

b) hybridizing said labeled nucleic acid molecules or fragments of said labeled nucleic acid molecules with a population of random nucleic acid molecules (page 37, third and fourth paragraph, where the random nucleic acid molecules are the probes listed in Table 2 on page 38); and

c) determining lymphocyte diversity of said subject by assessing hybridization of said labeled nucleic acid molecules with said population of random nucleic acid molecules (page 37, fourth paragraph; Fig. 3; Fig. 4; Table 1).

Regarding claims 2 and 3, Yoshida et al. teach the probes attached to microtiter plates (page 37, third paragraph).

Regarding claim 6, Yoshida et al. teach the probes attached to microtiter plates, therefore they inherently teach a plurality of different regions with different random nucleic acid molecules (page 37, third paragraph).

Regarding claims 13-15, Yoshida et al. teach T-cell receptor β chain sequences (Abstract; Table 2).

B) Yoshida et al. teach preparation of labeled DNA, but do not teach labeled RNA.

C) Regarding claim 1, Mahadevappa et al. teach hybridization of labeled RNA to oligonucleotide arrays to detect gene expression profiles (page 1136, paragraphs 2-6; Fig. 1 and 3).

Regarding claims 7 and 8, Mahadevappa et al. teach labeling of the RNA with phycoerythrin after hybridization to the array (page 1136, fourth paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used amplified RNA of Mahadevappa et al. in the method of detecting T-cell lymphocytes diversity of Yoshida et al. The motivation to do so was provide by Mahadevappa et al., as stated on page 1134, second paragraph:

"Gene expression monitoring methods that enable transcript measurement from very few cells, such as reverse transcriptase (RT) PCR, have the disadvantage of measuring only one or a few messages simultaneously7. Furthermore, PCR amplification can skew the relative abundance levels of the message by selective amplification."

Yoshida et al. are concerned with accurate determination of an abundance of TCR transcripts, and some of them are present at very low frequencies (see Fig. 3 and 4). Therefore, if the method were to be used to assess the influence of a pathological condition on the T-cell repertoire, using the RNA amplification of Mahadevappa et al. would provide assurance of accurate representation of the frequencies of different transcripts.

7. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al. (Immunogenetics, vol. 52, pp. 35-45, 2000; cited in the previous office action) and Mahadevappa et al. (Nature Biotechnol., vol. 17, pp. 1134-1136, 1999), as applied to claim 2 above, and further in view of Fulton et al. (Clin. Chem., vol. 43, pp. 1749-1756, 1997; cited in the previous office action).

A) The teachings of Yoshida et al. and Mahadevappa et al. are presented above. They teach solid support being a multiwell plate or chip, but do not teach beads or flow cytometry.

B) Fulton et al. teach multiplexing of analyte detection reaction using flow cytometry with fluorescently-labeled beads (Abstract; page 1749, second paragraph).

Regarding claim 4, Fulton et al. teach oligonucleotide probes immobilized on microspheres (page 1751, third seventh paragraph).

Regarding claim 5, Fulton et al. teach detection of nucleic acid hybridization by flow cytometry (page 1752, third paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used probes immobilized on beads and flow cytometry of Fulton et al. in the

detection of lymphocyte diversity of Yoshida et al. and Mahadevappa et al. The motivation to do is provided by Fulton et al. (page 1755, second and last paragraphs):

"These studies have demonstrated the ability of the FlowMetrix system to perform highly multiplexed assays for analysis of specific protein–protein interactions, such as immunoassays, and for analysis of specific DNA sequences. The system provides several advantages for analysis of biologically and medically relevant molecules, including speed, economy, and advanced analytical capabilities. The system reduces assay time by performing multiple analyses simultaneously rather than sequentially. The no-wash format of many microsphere-based assays, particularly in the final detection step, is considerably faster than microtiter-based assays that require multiple washing steps to remove excess reagents. In addition, the rapid kinetics of microsphere-based assays allow shorter incubation times than conventional solid phase assays. The reduced assay time also reduces labor costs for performing multiple analyses. Reagent usage for microsphere-based assays is 10- to 1000-fold less than microtiter-based assays. Multiplexing allows unique analysis of molecular interactions that can only be performed in a multiplexed format. "

The FlowMetrix system represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions, including basic research, clinical diagnostic testing, highthroughput drug screening, environmental testing, and agricultural testing. This system is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis. The system offers excellent sensitivity, precision, speed, and economy."

Rejections based on the Lebed et al. reference

8. Claims 1-3, 6, 7 and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lebed et al. (J. Biomol. Struct. Dynam., vol. 18, pp. 813-823, 2001; cited in the previous office

action) and Wang et al. (Nature Biotechnol., vol. 18, pp. 457-459, 2000; cited in the previous office action).

A) Regarding claim 1, Lebed et al. teach a method for determining lymphocyte diversity in a subject, said method comprising

a) providing labeled nucleic acid molecules from a population of said subject's lymphocytes, wherein each said labeled nucleic acid molecule encodes a lymphocyte receptor or a portion thereof (page 814, paragraphs 4-6; page 815, first paragraph; page 818, paragraphs 3-5);

b) hybridizing said labeled nucleic acid molecules or fragments of said labeled nucleic acid molecules with a population of random nucleic acid molecules (page 814, second paragraph; page 815, second and third paragraph; page 818, last paragraph); and

c) determining lymphocyte diversity of said subject by assessing hybridization of said labeled nucleic acid molecules with said population of random nucleic acid molecules (page 819; page 820; page 821; Table 1).

Regarding claims 2 and 3, Lebed et al. teach the probes attached to a chip (page 814, second paragraph).

Regarding claim 6, Lebed et al. teach the probes attached to chip, therefore they inherently teach a plurality of different regions with different random nucleic acid molecules (814, second paragraph).

Regarding claim 7, Lebed et al. teach fluorescent labels (page 815, first paragraph).

Regarding claims 13-15, Lebed et al. teach T-cell receptor β chain sequences (Abstract; page 814, paragraphs 4-6).

B) Lebed et al. teach labeled DNA molecules (page 815, first paragraph), but do not teach labeled RNA molecules.

C) Wang et al. teach hybridization of labeled RNA molecules to DNA chips (page 457; page 459, first and second paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used labeled RNA molecules of Wang et al. in the method of Lebed et al. The motivation to do so, provided by Wang et al., would have been that using RNA molecules permitted detection of low-abundance mRNAs and clinical samples (Abstract; page 458, fourth paragraph)

Lebed et al. disclose that there are possibly 10^6 to 10^7 different TCR transcripts (page 818, third paragraph; page 821, last paragraph), the abundance of which changes in diseased tissues, as discussed by Lebed et al. (page 818, first paragraph). Considering that the total RNA used for amplification was 300ng (page 814, fourth paragraph), a standard RT-PCR might not be sufficient to amplify low-abundance transcripts, as it is biased towards 3'-end amplification, as pointed out by Wang et al. Therefore one of ordinary skill in the art would be motivated to use the aRNA of Wang et al. instead of the cDNA of Lebed et al. for the determination of transcripts with low abundance.

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lebed et al. (J. Biomol. Struct. Dynam., vol. 18, pp. 813-823, 2001; cited in the previous office action) Wang et al. (Nature Biotechnol., vol. 18, pp. 457-459, 2000; cited in the previous office action), as applied to claims 1 and 7 above, and further in view of Allen et al. (U.S. Patent No. 6,017,710 A; cited in the previous office action).

A) Lebed et al. teach Texas Red as a fluorescent label (page 815, first paragraph), and Wang et al. teach Cy3 and Cy5 labels, but do not teach any of the labels listed in claim 8.

B) Allen et al. teach Texas Red is one of many fluorescent labels, including FITC, phycoerythrin or allophycocyanin (col. 14, lines 3-11).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used alternative fluorescent labels of Allen et al. in the method of Lebed et al. and Wang et al., since they are functionally equivalent compounds. As stated in MPEP 2144.06:

2144.06 Art Recognized Equivalence for the Same Purpose

>II. < SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE

In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958) (The mere fact that components are claimed as members of a Markush group cannot be relied upon to establish the equivalency of these components. However, an applicant's expressed recognition of an art-recognized or obvious equivalent may be used to refute an argument that such equivalency does not exist.); ** *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography. "This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor." 209 USPQ at 759.).

An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

10. No claims are allowed.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the

THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
January 15, 2009